Remarks

Claims 1-21 were pending. Applicants have canceled claims 9-21 without prejudice to Applicants' right to pursue their subject matter in this and other applications. Applicants have amended claim 1 to recite a method of diagnosing lupus nephritis in a mammal of interest selected from the group consisting of a human and a mouse, the method comprising the steps of detecting an expression level of midkine gene in a biological sample isolated from the mammal of interest, wherein the biological sample is selected from the group consisting of a kidney sample, a urine sample, and a blood sample; and using the expression level as a marker for lupus nephritis in the mammal of interest, wherein an elevated expression level indicates that the mammal has an increased likelihood of lupus nephritis. Support for the amendment to claim 1 is found in the original application at least, for example in paragraphs **[0014]**, **[0058]**, **[0064]**, **[0079]**, **[0080]** and **[0190]-[0195]** and in original claims 6 and 7. Claim 2 is amended to correct typographical errors and to alter claim dependency. Applicants have added new claim 22. Support for new claim 22 is found in the original application at least, for example, in original claim 1.

Applicants submit that the present amendment introduces no new matter into the application.

Applicants hereby affirm the election of the invention of Group II (*i.e.* claims 1-3 and 5-8) of the outstanding Office action. Accordingly, claims 1-3, 5-8 and 22 are under examination.

Information Disclosure Statement

Applicants thank Examiner Wong for considering the references in the information disclosure statement of July 8, 2005, with the exception of the International Search Report for PCT/US2003/33054, and for indicating this by initialing the references on the information disclosure statement. Applicants understand that the International Search Report postdates the present application. Applicants nevertheless believe that the information disclosure statement fully complied with 37 C.F.R. §§ 1.97-1.98 and MPEP § 609. 37 C.F.R. §§ 1.97-1.98 impose no requirement that the information provided in an information disclosure statement have existed at the time of the filing of the application. Indeed, MPEP § 609 expressly provides: "Once the minimum requirements of 37 CFR 1.97 and 37 CFR 1.98 are met, the examiner has an obligation

to consider the information. There is no requirement that the information must be prior art references in order to be considered by the examiner." Applicants have provided the International Search Report as the result of a search conducted on an application related to the present application and offer it for consideration to the extent it may inform or facilitate examination of the present application. Accordingly, Applicants respectfully request that Examiner Wong consider the International Search Report on that basis and so indicate by initialing the reference on the information disclosure statement.

Claim Objections

The Office action correctly objected to the misspellings in claim 2. Applicants have amended the claim to correct the misspellings and request withdrawal of the objection in view of the amendment.

35 U.S.C. § 112

The Office action rejected claims 1-3 and 5-8 under 35 U.S.C. § 112, first paragraph. The action acknowledged that the specification enables a method of diagnosing lupus nephritis (LN) in a mouse wherein the method comprises obtaining a kidney sample from a control mouse and a mouse with LN; determining the mRNA transcript level of midkine; comparing mRNA transcript level of midkine between a control and mouse with LN, wherein an increase in midkine mRNA transcript level, relative to the control, indicates that said mouse has an increased likelihood of LN. The action nevertheless disputed whether the application enables methods to diagnose systemic lupus erythematosus (SLE) or LN in any mammal by midkine expression level relative to the midkine expression level in a normal population.

Applicants request reconsideration and withdrawal of the rejection in view of the amendments to the claims.

As amended, the claims relate to methods of diagnosing lupus nephritis in a mammal of interest selected from the group consisting of a human and a mouse, the method comprising the steps of: detecting an expression level of midkine gene in a biological sample isolated from the mammal of interest, wherein the biological sample is selected from the group consisting of a kidney sample, a urine sample, and a blood sample; and using the expression level as a marker

for lupus nephritis in the mammal of interest, wherein an elevated expression level indicates that the mammal has an increased likelihood of lupus nephritis.

Methods of diagnosing lupus nephritis

The Office action acknowledged that the specification enables a method of diagnosing lupus nephritis. Applicants have amended the claims to recite a method of diagnosing lupus nephritis.

Using the expression level of midkine as a marker for lupus nephritis, wherein an elevated expression level indicates an increased likelihood of lupus nephritis

The Office action acknowledged that elevated levels of midkine expression can predict lupus nephritis, but noted that the claims were drawn to detecting the presence, absence, upregulation or downregulation of midkine expression. Applicants have amended the claims to recite using the expression level of midkine as a marker for lupus nephritis, wherein an elevated expression level indicates an increased likelihood of lupus nephritis.

In a mammal of interest selected from the group consisting of a human and a mouse

The Office action acknowledged that the specification enables a method of diagnosing lupus nephritis in a mouse. The Office action alleged, however, that the specification does not enable a method of diagnosing disease in "any mammal," stating that the claims included "the analysis of midkine levels of monkeys, sheep, dogs, pandas, lions, cows, cats, horses." Applicants have amended the claims to recite that the mammal is selected from the group consisting of a human and a mouse. As amended, the claims bear at least a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

The specification teaches all that is necessary to practice the invention—the detection of an expression level of midkine gene in a biological sample and its use as a marker for lupus nephritis. The Office action agrees that the specification teaches how to detect an expression level of midkine gene. The specification also teaches how to use the expression level of midkine gene as a marker for lupus nephritis, wherein an elevated expression level indicates an increased likelihood of lupus nephritis. The Office action nevertheless questions whether the method

would be useful and effective in diagnosing lupus nephritis in mammals other than mice, stating that "an animal model may not be an accurate representation of another animal's response to lupus" (Office action, page 11), citing Kotzin (1997) J. Clin. Invest. 99(4):557-558 ("Kotzin") as support. Applicants disagree with this characterization of Kotzin. Kotzin comments on the identification of a human locus associated with SLE in an analysis of sibpairs but cautions, as noted in the Office action, that an initial mapping in a complex trait could reflect a false positive finding. Kotzin does not conclude that animal models are not useful or accurate; does not conclude that the human locus differs from the susceptibility locus identified with a mouse model; and does not conclude that an understanding of a mouse susceptibility locus is meritless in understanding human disease. Quite the contrary, in fact: Kotzin teaches that "rodent models of disease have contributed greatly to understanding the immunopathogenesis of different autoimmune diseases, including SLE, type 1 diabetes, and multiple sclerosis" (Kotzin, p. 557). As the Office action indicates, Kotzin points out that animal models provide reduced genetic variability, facilitating genetic studies—Kotzin does not, however, conclude that the genetic studies are less useful or less applicable to other mammals as a result. Quite the contrary, in fact: Kotzin teaches that "the results from animal models could be useful in . . . major ways," including testing the identified genes for linkage or association with the human disease (Kotzin, p. 557). Kotzin encourages the use of animal models and the use of their results in human disease.

Accordingly, Applicants submit that it is well within the level of skill in the art (a level acknowledged in the Office action to be high) to apply methods and knowledge from animal studies to humans, despite the differences between controlled animal studies and observed human diseases. The USPTO has made clear in the context of the utility requirement that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials" (MPEP § 2107.03(IV)). Experimentation applying the results of animal studies to humans is routine and, therefore, not undue. As currently amended, the claims therefore bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Wherein the biological sample is selected from the group consisting of a kidney sample, a urine sample, and a blood sample

The Office action acknowledges that the specification enables the use of kidney samples, but alleges that the specification does not enable the use of "any biological sample." Applicants have amended the claims to recite a biological sample selected from the group consisting of a kidney sample, a urine sample, and a blood sample. Applicants note that urine and blood are fluids that contact the kidney and are fluids that have been demonstrated to carry other protein and nucleic acid markers of other diseases—any experimentation to investigate midkine levels in blood and urine would be reasonable and routine. As amended, the claims therefore bear at least a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Caselaw

The Federal Circuit has recently spoken to the application of the enablement requirement in the biotech context in Invitrogen v. Clontech (Fed. Cir. 2005). The court held that "the enablement requirement is met if the description enables any method of making and using the invention" (slip. op. at 28). The court held that Invitrogen's claims encompassing deletion mutations and point mutations were "not invalid for lack of an enabling disclosure on point mutation" (slip. op. at 29) because "Invitrogen fully described an operable method for achieving the claimed mutation" (slip. op. at 29) by deletion. As the court held:

> Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. Such narrow rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain.
>
> (slip. op. at 29)

Here, the claims are even more clearly enabled than they were in Invitrogen. Even though enablement "does not require the inventor to foresee every means of implementing an invention" (Invitrogen, slip. op. at 29), the inventors here did indeed foresee and describe implementing their invention by detection of an expression level of midkine gene in a kidney, urine, or blood sample isolated from a human and using the expression level as a marker for lupus nephritis. Accordingly, the present claims bear at least a reasonable correlation to the

scope of enablement provided by the specification to persons of ordinary skill in the art and Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 102

The Office action rejected claims 1, 2, 5, 6 and 8 as allegedly anticipated by Mishima *et al.* (1997) Neuroscience Lett. 233:29-32 ("Mishima"). Applicants have amended independent claim 1 to recite a method of diagnosing lupus nephritis in a mammal of interest; the method comprises detecting an expression level of midkine gene in a kidney sample, a urine sample, or a blood sample and using the expression level as a marker for lupus nephritis. Mishima does not teach a method of diagnosing lupus nephritis; does not teach detecting an expression level of midkine gene in a kidney sample, a urine sample, or a blood sample; and does not teach using the expression level as a marker for lupus nephritis. Accordingly, Mishima does not anticipate claim 1 or any other pending claim, each of which depend directly or indirectly from claim 1. Applicants therefore request withdrawal of the rejection in view of the amended claims.

35 U.S.C. § 103

The Office action rejected claims 1-3 and 5-8 under 35 U.S.C. § 103 as allegedly unpatentable over Swiniarski *et al.* (2001) FASEB J. 15(5):A1214 ("Swiniarski") in view of Takada *et al.* (1997) J. Biochem. 122:453-458 ("Takada") in further view of Affymetrix GeneChip Murine 11K set (Product manual, 1998) ("Affymetrix Murine 11K"). Applicants request reconsideration and withdrawal of the rejection to the extent it is maintained against the amended claims.

As amended, the claims relate to methods for diagnosing lupus nephritis in a mammal of interest; the methods comprise detecting an expression level of midkine gene and using the expression level as a marker for lupus nephritis in the mammal of interest.

The cited references do not render the claimed invention obvious because they do not suggest the desirability of using the expression of midkine as a marker for lupus nephritis and

provide no reasonable expectation of success that expression of midkine can be used as a marker for lupus nephritis.

Of the three cited references, only Swiniarski appears to mention lupus nephritis. Swiniarski does not mention midkine or its expression as a marker for lupus nephritis. Swiniarski mentions that expression of approximately 11,000 murine genes was evaluated using Affymetrix oligonucleotide arrays; that some were differentially regulated in disease free and diseased kidney; and that among the disease associated genes are genes related to T and B lymphocyte function, antigen processing and presentation, complement, and fibrosis. The Office action alleges that one skilled in the art would have been motivated to use the Affymetrix Murine 11K in combination with Swiniarski, permitting the simultaneous screening of a multitude of genes, including midkine. Even if that were true, however, the cited references provide no motivation to use midkine as a marker for lupus nephritis and provide no reasonable expectation that midkine would be useful as a marker for lupus nephritis. Accordingly, the cited references cannot render the amended claims obvious.

Applicants therefore request withdrawal of the rejection.

Conclusion

Examiner Wong is invited to telephone the undersigned attorney to discuss any remaining issues.

Respectfully submitted,

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Reg. No. 48,645

Brian A. Fairchild, Ph.D.
Attorney for Applicants
Kirkpatrick & Lockhart Nicholson Graham LLP
State Street Financial Center
One Lincoln Street
Boston, Massachusetts 02111

Tel. No.: (617) 261-3169
Fax No.: (617) 261-3175
Customer Number: 054623